DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Stephanie Davis
Associate Director, Regulatory Affairs
Johnson & Johnson, Consumer & Personal Products Worldwide
Division of Johnson & Johnson Consumer Companies, Inc.
199 Grandview Road
Skillman, NJ 08558-9418

RE: NDA# 21-385
ERTACZO™ (sertaconazole nitrate) Cream, 2%
MACMIS ID # 17795

Dear Ms. Davis:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a journal advertisement (08DD0049) for ERTACZO™ (sertaconazole nitrate) Cream, 2% (Ertaczo) submitted under cover of Form FDA-2253 by Johnson & Johnson. This journal advertisement broadens the approved indication, contains unsubstantiated efficacy claims about the product, and omits important risk information. Therefore, this piece misbrands Ertaczo in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(n) and 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (vii), (xviii) & (e)(7)(i).

Furthermore, you failed to submit the journal advertisement to FDA under cover of Form FDA-2253 at the time of its initial publication, as required by 21 CFR 314.81(b)(3)(i).

Background

According to the INDICATIONS AND USAGE section of its FDA-approved product labeling (PI), Ertaczo is indicated for:

> the topical treatment of interdigital tinea pedis in immunocompetent patients 12 years of age and older, caused by *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum*.

Additionally, the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections of the PI state (in relevant part):

> **CONTRAINDICATIONS:** ERTACZO™ Cream, 2%, is contraindicated in patients who have a known or suspected sensitivity to sertaconazole nitrate or any of its components or to other imidazoles.
>
> **WARNINGS:** ERTACZO™ Cream, 2%, is not indicated for ophthalmic, oral or intravaginal use.

PRECAUTIONS:
General: . . . .
If irritation or sensitivity develops with the use of ERTACZO™ Cream, 2%, treatment should be discontinued and appropriate therapy instituted.

Diagnosis of the disease should be confirmed either by direct microscopic examination of infected superficial epidermal tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Physicians should exercise caution when prescribing ERTACZO™ Cream, 2%, to patients known to be sensitive to imidazole antifungals, since cross-reactivity may occur.

Broadening of Indication

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. The journal ad includes the claims, "In the Treatment of Tinea Pedis" and "TINEA STOPS HERE." These claims misleadingly suggest that Ertaczo is approved for all patients, regardless of age or immune status, who have any form of tinea pedis caused by any organism, when this is not the case. Ertaczo is "indicated for the topical treatment of **interdigital** tinea pedis **in immunocompetent patients 12 years of age and older, caused by: *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum***" (bolded emphasis added). As such, Ertaczo is not approved for patients under 12 years of age, patients who are immunocompromised, patients with other forms of tinea pedis (e.g., moccasin-type), or patients with interdigital tinea pedis caused by organisms other than the dermatophytes listed in the indication for this product.

Unsubstantiated Efficacy Claims

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The journal ad includes the claim "**Crush. Kill. Destroy.**" (emphasis in original) in large, bolded, bright-orange type in conjunction with the claim, "Sertaconazole Nitrate **Wipes Out** Tinea With a Three-Pronged Attack" (emphasis added). These claims are misleading because they greatly overstate the efficacy of this product. According to the CLINICAL STUDIES section of the PI, two randomized, double-blind clinical trials were conducted in patients 12 years and older with interdigital tinea pedis. In these studies, Ertaczo provided complete cure rates of **13.1%** (Ertaczo) vs. 3.3% (vehicle), a 9.8% effect, and **27.2%** (Ertaczo) vs. 4.9% (vehicle), a 22.3% effect. Although these results show modest effectiveness, they clearly do not support the claims that Ertaczo "wipes out" or crushes, kills, and destroys tinea infections.

Furthermore, underneath the claim "Sertaconazole Nitrate Wipes Out Tinea With a Three-Pronged Attack," the journal ad presents the following three bullets:

- "Fungicidal[1,2]"
- "Anti-Inflammatory[*3,4]"
- "Anti-Itch[+4]"

This presentation is misleading for numerous reasons. First, it suggests that sertaconazole, the active ingredient in Ertaczo, is fungicidal against the dermatophytes Ertaczo is approved to treat (*Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum*). The journal ad cites "Data on file" and the Pfaller et al. article to support this claim. However, these references discuss fungicidal/fungistatic activity of sertaconazole against <u>yeasts</u>, not the dermatophytes that Ertaczo has been approved to treat when they are the cause of interdigital tinea pedis. We are not aware of any data that support the claim that Ertaczo is fungicidal in the treatment of interdigital tinea pedis caused by the above listed dermatophytes.

Second, this presentation, along with the claim appearing below it that "Anti-Inflammatory Actions (*in vitro*) May Enhance Symptom Relief,[**5]" suggests that Ertaczo has anti-inflammatory properties. The journal ad cites the Lyte, et al., Liebel, et al., and Sur, et al. articles to support these claims. According to these references, this purported effect has only been described in rodent, human lymphocyte, and human keratinocyte studies. We are not aware of **any** clinical studies that document an effect on human inflammatory responses in diseased skin, or the clinical significance of such an effect. Thus, these studies do not constitute substantial evidence to support the claims that Ertaczo affects anti-inflammatory actions that may enhance symptom relief.

Lastly, this presentation suggests that Ertaczo has anti-itch properties. The journal ad cites the Liebel et al. article to support this claim. The article describes the effects of sertaconazole on T cell lymphocytes in nonclinical mouse studies, including a mouse study on itching. The article does not present any clinical data in human patients with tinea pedis,

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[1] Data on file, OrthoNeutrogena.

[2] Pfaller MA, Sutton DA. Review of in vitro activity of sertaconazole nitrate in the treatment of superficial fungal infections. *Diagn Microbiol Infect Dis*. 2006;56(2):147-52.

[*] *In vitro* data.

[3] Lyte P, Liebel F, Garay M, Southall M. Effects of sertaconazole nitrate on T-cell activation, irritant dermatitis and contact hypersensitivity. Presented at: American Academy of Dermatology 63rd Annual Meeting; February 18-22, 2005; New Orleans, La.

[4] Liebel F, Lyte F, Lyte P, Garay M, Babad J, Southall MD. Anti-inflammatory and anti-itch activity of sertaconazole nitrate. Arch Dermatol Res. 2006;298(4):191-199.

[+] Data demonstrated in *in vivo* animal models.

[**] *In vitro* data do not necessarily correlate with a clinical outcome.

[5] Sur R, Babad JM, Garay M, Liebel FT, Southall MD. Anti-inflammatory activity of sertaconazole nitrate in mediated via activation of a p38-COX-2-PGE_2 pathway. J Invest Dermatol. Advance online publication. July 19, 2007;dol:10.1038/sj.jid.5700972. Available at: http://www.nature.com/jid/journal/vaop/ncurrent/abs/5700972a.html;jsessionid=60390E24E7E1F7F4DC0905A6818EA7AF. Accessed July 30, 2007.

or clinical data that relates to the anti-pruritic effects of Ertaczo on humans. As such, the data provided in this reference do not constitute substantial evidence to support this clinical benefit claim.

We note that the journal ad presents the following information as footnotes to the anti-inflammatory and anti-itch claims: "*In vitro* data," "Data demonstrated in *in vivo* animal models;" and "*In vitro* data do not necessarily correlate with a clinical outcome." However, these footnotes do not mitigate the misleading messages created by these claims.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested by the materials. Although the journal ad presents some of the adverse events associated with Ertaczo, it fails to include the Contraindication or any of the Warnings and Precautions information for this drug product (see Background section above). Because the advertisement omits these important risks, it misleadingly suggests that Ertaczo is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Failure to Submit Under Form FDA-2253

FDA regulations require companies to submit specimens of any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use) and is required to include a copy of the product's current professional labeling. A copy of the journal ad was not submitted to FDA on Form FDA-2253 at the time of its initial publication as required by 21 CFR 314.81(b)(3)(i). Rather, it was submitted on August 21, 2008, six months after the dissemination date listed on the FDA-2253 form of Feb 2008. We are also aware that prior to the August 2008 submission to FDA, this advertisement appeared in the July 2008 issue of *Dermatology Times* (Volume 29, Number 7, Page 69).

Conclusion and Requested Action

For the reasons discussed above, your professional journal advertisement misbrands Ertaczo in violation of the Act, 21 U.S.C. 352(n) & 321(n), and FDA's implementing regulations. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (vii), (xviii) & (e)(7)(i). Furthermore, you failed to submit the journal advertisement to FDA under cover of Form FDA-2253 at the time of its initial publication, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Johnson & Johnson immediately cease the dissemination of violative promotional materials for Ertaczo such as those described above. Please submit a written response to this letter on or before September 4, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Ertaczo as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such

violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 17795 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Ertaczo comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Andrew S.T. Haffer, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Catherine B. Gray, PharmD
Professional Group Leader
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CATHERINE B GRAY
08/21/2009